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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,457	12/06/2000	Ian Popoff	RTS-0182	1220

7590 07/16/2003

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,457	POPOFF ET AL	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed May 1, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed November 11, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Response to Arguments

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dualan et al., in view of Taylor et al., Baracchini et al, Hayes et al. and Krishnamoorthy et al. This rejection is based on the previous rejection of record, but has been changed in accordance with applicants' amended claims. Those elements of applicants arguments that are considered to be relevant to the instant rejection are addressed below. Accordingly, applicant's arguments filed May 1, 2003 have been fully considered but they are not persuasive, particularly in light of the rejection as newly stated below.

The invention of the above claims is drawn to antisense compounds, their internucleoside linkages, sugar, nucleobase, and 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents or delivery systems thereof that target and inhibit the expression of DDB p127.

Dualan et al. teach the cDNA sequence encoding DDB p127. Dualan et al. does not teach antisense sequences comprising sugar, nucleobase, and 2' modifications, chimeras, and

compositions comprising said compounds and pharmaceutically acceptable diluents or delivery systems thereof.

Taylor et al. teaches the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein. Taylor et al. also teaches that with modern software and high-affinity chimeras, that only 3-6 oligos need to be screened in order to find one that inhibits gene expression by 66-95% *in vitro*.

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Baracchini et al. also teach targeting specific regions of a gene including the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, and demonstrate methods necessary to achieve antisense-mediated gene inhibition.

Hayes et al. teach that DDB p127 stimulates E2F1 -activated transcription of cell-cycle related genes that are essential for DNA replication and cell cycle progression (page 246).

Krishnamoorthy et al. teach antibody inhibition of DDB p127 as a means of testing the function of DDB p127 (Biochemistry 1997. 36(4)960-969, newly cited).

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence of Dualan et al. to make antisense sequences as taught by Taylor et al. for inhibition of DDB p127 expression, and further, it would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini et al. into said antisense compounds.

One would have been motivated to make such compounds because Krishnamoorthy et al. teach antibody inhibition of DDB p127 as a means of testing the function of DDB p127, and because Hayes et al. teach that DDB p127 stimulates E2F1-activated transcription of cell-cycle

related genes that are essential for DNA replication and cell cycle progression (page 246). Since Krishnamoorthy et al. teach the value of inhibiting the DDB p127 target as a means of understanding DDB p127 function, one of ordinary skill would have been motivated to make and use alternative inhibitors of DDB, such as the antisense inhibitors as taught by Taylor. Furthermore, because Hayes et al. teach that DDB regulates a gene that controls cell cycle progression, one would have been motivated to further characterize the function of DDB p127 as it pertains to undesireable cell-proliferation.

One would have been motivated to target the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, as recited in the instant claim 1, because Baracchini et al. teach that these sites are preferred targeting sites in designing antisense oligos. Furthermore, one would have been motivated to modify said antisense compounds as taught by Baracchini et al., because Baracchini et al. teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation.

Finally, one would have a reasonable expectation of success given that Taylor teaches that antisense-mediated inhibition of known sequences *in vitro* is routine to one of ordinary skill in the art, and since Baracchini et al. teach the successful synthesis of modified antisense compounds such that the activity of said compounds is enhanced. Therefore one of ordinary skill in the art would have been motivated to design specific inhibitors to DDB p127 such as the antisense molecules as presently claimed.

Regarding applicants' previous arguments, it was asserted that Hayes et al. does not provide motivation to inhibit applicants' instant target, because Hayes et al. disclose only a role for the p48 subunit in regulating the activity of E2F1, and do not teach or suggest any role for the

instantly contemplated p127 subunit of Damage-specific DNA binding protein 1 (DDB1) in such regulation. This is not convincing, because Hayes clearly teach that both subunits are required for optimal binding to the E2F1 (p. 243, bridging para. to 244, fig. 5). Moreover, co-transfection of both subunits is required to stimulate E2F1 transcription; importantly, transfection of any one subunit was not able to induce E2F1 transcription (p. 246, lines 5 and 6). Such results clearly indicate that targeting either subunit of DDB1 would be sufficient to interfere with E2F1-mediated transcription, and is contrary to Applicants' assertion that Hayes only provides motivation to target the p48 subunit. In summary, Hayes et al. provide motivation to target the instantly claimed p127 subunit of DDB1, because Hayes et al. teach that both subunits are required to stimulate E2F1-mediated transcription.

Applicants' state that, when viewed alone, none of Dualan et al., Baracchini et al., Hayes et al., or Taylor et al. teach or suggest antisense compounds targeted to the specific regions of the DDB p127 transcript of SEQ ID NO: 3 as presently claimed. This argument is not adopted. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is acknowledged that the references when viewed individually do not teach the presently claimed invention; however, the test for obviousness is what the *combined* teaching of the prior art would have suggested to those of ordinary skill in the art. As indicated above, one of ordinary skill in the art would have been motivated to make antisense oligonucleotides, because the prior art teaches inhibitors of DDB p127 function, and that DDB stimulates a gene that controls cell cycle progression. Therefore,

one would have been motivated to make other inhibitors, such as the instantly contemplated antisense molecules. Moreover, because Baracchini et al. and Taylor et al. teach that synthesizing and using antisense oligos to inhibit transcripts of known sequence is routine to one of ordinary skill in the art, this combination also provides a reasonable expectation of success which render the invention of the claims above obvious under 35 U.S.C. § 103(a).

Applicants also argue that Taylor et al., while teaching that antisense can be designed to inhibit any gene target provided its sequence is known, does not teach that such sequences would be active as inhibitors of gene expression. This assertion is not convincing, because as argued above, one of ordinary skill in the art would have expected to have had a reasonable expectation of success in formulating and using such oligonucleotides. Taylor et al. cites that only 3-6 sequences need to be screened in order to find one that inhibits 66-95% *in vitro*, which is well within the capabilities of one of ordinary skill. As such, Taylor et al. provides no reason to doubt that such antisense compounds can be designed to work *in vitro*, and actually points to a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
July 9, 2003

KAREN LACOURCIERE
PATENT EXAMINER